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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,049	10/02/2003	Andreas Menrad	SCH-1832-D1	7768

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,049	MENRAD ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/942,117.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/2/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 26-33 are pending.

2. Applicant's election with traverse of Group I, claims 26-33 drawn to a process for screening antibodies that bind to a receptor of the ED_b-fibronectin domain, wherein the response is mediated by a receptor of the ED_b-fibronectin and SEQ ID NO: 4 as the species filed on 9/07/04, is acknowledged.

Applicant's traversal is on the grounds that the linking claims relate to screening of compound in general, which is the norm for such screening claims. The mere fact that various kinds of compounds can be screened and are the subject of various claims cannot possibly sensibly require a restriction.

Upon reconsideration, Examiner has rejoined Groups II-V with elected Group I to cover antibodies, peptides, low molecular compounds, aptamers and Spiegelmers and the species of SEQ ID NOs: 1-4. The restriction requirement is hereby withdrawn.

4. The specification on page 1 should be amended to reflect the status of 09/942,117 and the relationship between 09/942,117 and the instant application.

5. Claims 26-33 are objected to because they are dependent on canceled claim 1 and should be written as independent claims.

6. Claim 26 is objected to for the following informalities: the word "Comparison" uses the upper case letter instead of the lower case letter.

7. Claims 28 and 31 are objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim.

8. It is improper to recite "compounds", "antibodies", "antibody fragments", "peptides", "low molecular compounds", "aptamers: and "Spiegelmers" in claims 26 and31-32 as the claims should recite the singular form.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 26-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 26 is indefinite because it is unclear whether the "receptor of the ED_b-fibronectin domains" is the same as or different from the "protein" of canceled claims 1-10.

B. Claim 33 is indefinite in that recitation of the "fragment thereof". It is unclear if this "fragment thereof" refers to any scFv fragment or it is limited to fragments containing the antigen-binding domain of the antibody.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 26-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a process for screening compounds that bind to any "receptor of the ED_b-fibronectin domain, whereby the process comprises comparison of any "response of cells" in the presence of one or more of these compounds with the "control response" of said cells in the absence of these compound, whereby the cells express a protein according to one of canceled claims 1-10 or comprise a nucleic acid that codes for this proeitn, and whereby the "response" or the "control response" is mediated by a receptor of the ED_b-fibronectin domains in claim 26, whereby the response or the control response comprises the adherence of cells to surfaces that are coated with the "ED_b-fibronectin domains" or "portions thereof" in claim 27, wherein a binding region of the ED_b-fibronectin domains comprises sequences SEQ ID NO:1-4 or "portions thereof" in claim 28, wherein the response or the control response comprises the proliferation of cells on surfaces that are coated with the EDb-fibronectin domains or portions thereof in claim 29, wherein the response or the control response comprises the proliferation, migration and differentiation of endothelial cell in a collagen matrix that is mixed with the EDb-fibronectin domains or portions thereof in claim 30, whereby the compounds are antibodies, artificial antibodies, antibody fragments, peptides, low molecular compounds, aptamers and Spiegelmers in claim 31, wherein the antibodies are recombinant antibodies in claim 32, wherein the antibodies are scFv and fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to screening a compound that modulates a response mediated by ED_b receptor.

One cannot extrapolate the teachings of the specification to the scope of the claims because the specification on pages 37-38 teaches that the ED_b-fibronectin receptor is $\alpha2\beta1$ integrin, therefore a compound that binds to either, $\alpha2$, $\beta1$ or the $\alpha2\beta1$ complex would modulate the claimed response. However, Chen et al (Exp Cell Res. 1996 Feb 25;223(1):9-19) teach that studies using neutralizing anti-$\beta1$ antibodies (e.g., "Lenny" antiserum or CSAT monoclonal antibody) have ruled out any possible involvement of $\beta1$ integrin in adhesion to ED_b recombinants, the antibodies did not inhibit cell adhesion to pFN (see page 19, last paragraph in particular).

Claim 26 recites that the compounds bind to "a receptor of the ED_b-Fibronectin domains", however, besides the $\alpha2\beta1$ integrin receptor, the specification has not provided sufficient biochemical information that distinctly identifies such "a receptor of the ED_b-Fibronectin domains". While any receptor of the ED_b-Fibronectin domains may have some notion of the activity, claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such receptors, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any receptor of the ED_b-Fibronectin domains that can be used for screening assay. The instant claims further encompass in their breadth "ED_b-fibronectin domains", however, the specification on page 4, 3rd ¶ discloses that the ED_b domain is a repetition sequence of type III that comprises 91 amino acids and has an extremely high sequence homology between rate and chicken fibronectin. Therefore, the skill artisan would not know all the ED_b domains recited in the specification other than the fibronectin's alternative spliced ED_b (EIIIB) domain mono-repeat of SEQ ID NO: 4. Furthermore, claims 26 recites a "response of cells", the skilled artisan would not know what response to screen for. Further, since a response can be either upregulatiion or down regulation, such responses are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints. One skilled in the art cannot use any response effect as indicators of a test to determine compound's response potential.

The outcome of the response effect does not correlate with the end result to identify compound modulators of response. There is no correlation between any response effect (functional effect), ED_b-fibronectin domains, the compounds to be screened and any response. There is insufficient guidance in the specification to assist the outcome of any functional effect and its correlation to a response, upon contacting the compounds and ED_b-fibronectin domains.

Claims 27-30 recites "ED_b-fibronectin domains or portions thereof", such a recitation does not require that the full length sequence set forth in ED_b-fibronectin domain; but rather encompasses any amino acid sequence comprising either the full length of ED_b-fibronectin domain or *any subsequence*. However, the specification does not appear to have provided sufficient guidance as to which subsequences of ED_b-fibronectin domain would share the function of binding to $\alpha2\beta1$, other than the ED_b-fibronectin domain of SEQ ID NO:4 and a portion consisting of SEQ ID NOs: 1-3, the specification fails to provide. Neither does the specification appear to have

provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of ED_b-fibronectin would have the function of the full length of ED_b-fibronectin domain.

Claim 28 recites the "ED_b-fibronectin domains comprises sequences SEQ ID NOs: 1-4 or portions thereof", however, the term "comprising" is an open-ended and expand the polypeptide of SEQ ID NO: 1-4 to include additional non disclosed amino acids on either or both sides of the N- and C- terminal of SEQ ID NO:1-4.

Claims 29-30 recite that response is proliferation, however, Ffrench-constant et al (Development. 1989 Jun;106(2):375-88) teach that during development EIIIB (EDb) was preferentially excluded after the completion of growth and that the EIIIB has a role in the migration and/or proliferation of embryonic cells prior to their terminal differentiation (see abstract in particular). Further, the specification on page 22, under Fig. 2 discloses that ED-B had no action on cell proliferation in the absence of bFGF.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. Claims 26-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a process for screening compounds that bind to any "receptor of the ED_b-fibronectin domain, whereby the process comprises comparison of any "response of cells" in the presence of one or more of these compounds with the "control response" of said cells in the absence of these compound, whereby the cells express a protein according to one of canceled claims 1-10 or comprise a nucleic acid that codes for this proeitn, and whereby the "response" or the "control response" is mediated by a receptor of the ED_b-fibronectin domains in claim 26, whereby the response or the control response comprises the adherence of cells to surfaces that are coated with the "ED_b-fibronectin domains" or "portions thereof" in claim 27, wherein a binding region of the ED_b-fibronectin domains comprises sequences SEQ ID NO:1-4 or "portions thereof" in claim 28, wherein the response or the control response comprises the proliferation of cells on surfaces that are coated with the EDb-fibronectin domains or portions thereof in claim 29, wherein the response or the control response comprises the proliferation, migration and differentiation of endothelial cell in a collagen matrix that is mixed with the EDb-fibronectin domains or portions thereof in claim 30, whereby the compounds are antibodies, artificial antibodies, antibody fragments, peptides, low molecular compounds, aptamers and

Spiegelmers in claim 31, wherein the antibodies are recombinant antibodies in claim 32, wherein the antibodies are scFv and fragments thereof.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (a receptor of the ED_b-fibronectin domains/a protein) to describe the claimed genus, nor does it provide a description of structural features that are common to species (a receptor of the ED_b-fibronectin domains/a protein). The specification provides no structural description of a receptor of the ED_b-fibronectin domains/a protein other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed receptors looks like. The specification's disclosure is inadequate to describe the claimed genus of a receptor of the ED_b-fibronectin domains/a protein.

Further, Applicant has disclosed only amino acid of SEQ ID NO: 1-4; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 26-28 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (Exp Cell Res. 1996 Feb 25;223(1):9-19).

Chen et al teach a method for screening for any possible involvement of β1 integrin (a receptor of the ED_b-fibronectin domains) in adhesion to ED_b recombinants using neutralizing anti-β1 antibodies (e.g., "Lenny" antiserum or CSAT monoclonal antibody) (a compound that binds a receptor of the ED_b-fibronectin domains), the antibodies did not inhibit cell adhesion to pFN (see page 19, last paragraph in particular) in claim 26. While Chen et al is silence as to compare the response of the cells with the control response, such a comparison is inherent step in the method of determining whether the antibody would inhibit cell adhesion to pFN. Chen et al teach that the recombinant proteins were adsorbed to 96-well tissue culture plates at various dilutions at room temperature fro 1 hr (surfaces that are coated with the ED_b-fibronectin domains or portions thereof) in claim 27 (see page 10, 2nd col., last ¶ in particular). Chen et al teach that seven constructs encoding all possible combinations of ED_b and it neighboring type III repeats (see Fig 1 in particular) such ED_b constructs would comprise claimed SEQ ID NOs:1-4 in claim 28. The reference anti-β1 antibody would bind to a receptor heterodimer of all alpha integrin subunits that makes heterodimer with β1 including α2.

The reference teachings anticipate the claimed invention.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 26-28, 31 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (Exp Cell Res. 1996 Feb 25;223(1):9-19) in view of Bird *et al* (1988).

The teachings of Chen et al reference, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a recombinant a single chain antibody in claims 32-33.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light –chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particlular)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Chen et al as a recombinant single chain antibody as taught by the Bird *et al* and utilize it in the method of screening.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground since the single chain antibody lack the Fc portion as taught by Bird *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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